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EXAMINER	
MYERS, CARLA J	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,278	LANCET ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24,27,28 and 30-34* is/are pending in the application.

4a) Of the above claim(s) *1-22,27 and 30-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23, 24, 28 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendment filed July 26, 2007. Applicant's arguments have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn.

This action is made final.

2. Claims 1-24, 27, 28, and 30-34 are pending. Claims 1-22, 27 and 30-31 are withdrawn from consideration as being dawn to an invention non-elected without traverse in the reply filed on January 4, 2007 is acknowledged.

Claims 23, 24, 28 and 34 have been examined herein.

3. The declaration under 37 CFR 1.132 filed July 26, 2007 is insufficient to overcome the rejection of claims 23, 24, 28 and 34 under 35 USC 101 and 112 first paragraph as set forth in the last Office action for the reasons discussed below.

Maintained Rejections

Claim Rejections - 35 USC § 101

4. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Definitions: [from UTILITY GUIDELINES TRAINING MATERIALS; repeated from http://www.uspto.gov/web/menu/utility.pdf]

"Credible Utility" - Where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as being "wrong". Rather, Office personnel must determine if the assertion of utility is

credible (i.e., whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided). An assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based is inconsistent with the logic underlying the assertion. Credibility as used in this context refers to the reliability of the statement based on the logic and facts that are offered by the applicant to support the assertion of utility. A *credible* utility is assessed from the standpoint of whether a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for such use. For example, no perpetual motion machines would be considered to be currently available. However, nucleic acids could be used as probes, chromosome markers, or forensic or diagnostic markers. Therefore, the credibility of such an assertion would not be questioned, although such a use might fail the *specific* and *substantial* tests (see below).

"Specific Utility" - A utility that is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention. For example, a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be *specific* in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

"Substantial utility" - a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. On the other hand, the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":

A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.

B. A method of treating an unspecified disease or condition. (Note, this is in contrast to the general rule that treatments of specific diseases or conditions meet the criteria of 35 U.S.C. 101.)
C. A Method of assaying for or identifying a material that itself has no "specific and/or substantial utility".
D. A method of making a material that itself has no specific, substantial, and credible utility.
E. A claim to an intermediate product for use in making a final product that has no specific, substantial, and credible utility.

Note that "throw away" utilities do not meet the tests for a *specific* or *substantial* utility. For example, using transgenic mice as snake food is a utility that is neither specific (all mice could function as snake food) nor substantial (using a mouse costing tens of thousands of dollars to produce as snake food is not a "real world" context of use). Similarly, use of any protein as an animal food supplement or a shampoo ingredient are "throw away" utilities that would not pass muster as specific or substantial utilities under 35 U.S.C. ' 101. This analysis should, or course, be tempered by consideration of the context and nature of the invention. For example, it a transgenic mouse was generated with the specific provision of an enhanced nutrient profile, and disclosed for use as an animal food, then the test for specific and substantial *asserted* utility would be considered to be met.

"Well established utility" - a specific, substantial, and credible utility which is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art. "Well established utility" does not encompass any "throw away" utility that one can dream up for an invention or a nonspecific utility that would apply to virtually every member of a general class of materials, such as proteins or DNA. If this is the case, any product or apparatus, including perpetual motion machines, would have a "well established utility" as landfill, an amusement device, a toy, or a paper weight; any carbon containing molecule would have a "well established utility" as a fuel since it can be burned; any protein would have well established utility as a protein supplement for animal food. This is not the intention of the statute.
See also the MPEP at 2107 - 2107.02.

5. Claims 23, 24, 28 and 34 are rejected under 35 U.S.C. 101 because the claimed invention lacks a credible, substantial, specific or well-established utility.

The claims are drawn to methods for typing a subject for the presence or absence of an allelic variant of an olfactory receptor gene. With respect to the elected invention, the claims are directed to methods wherein the olfactory receptor gene consists of SEQ ID NO: 81 and wherein the oligonucleotide of SEQ ID NO: 29 is used to detect the presence of a C to T polymorphism at SNP position 691. The claimed methods are not supported by either a specific and substantial asserted utility or a well-established utility. The specification fails to provide objective evidence of a specific activity for the claimed olfactory receptor nucleic acids containing allelic variants polymorphisms and thereby a utility for the methods for detecting said allelic variants.

Regarding the elected invention, the specification (Table 5 and 6) teaches that the OR11H7p gene of SEQ ID NO: 81 contains a C to T polymorphism at position 691, resulting in the introduction of a stop codon. The OR11h7p nucleic acid is characterized as a segregating pseudogene in Table I (page 62) of provisional application 60/374,508. The specification further teaches the frequency of the intact and disrupted allele in Table 5 in African American subjects and in non-African American subjects. In Table 5, the specification also sets forth a number of additional olfactory receptor genes, an allelic variant form of said genes and the frequency of intact and disrupted alleles in African American subjects and in non-African American subjects.

The specification (page 1) teaches that there are about 400 functional olfactory receptor (OR) genes in humans and that the diversified OR repertoire is needed to allow individuals to detect and discriminate between thousands of different odorant molecules. The specification (page 2) also teaches that ORs interact with a diverse array of volatile molecules and that this binding pattern generates a unique

combinatorial code for each odorant that enables an organism to distinguish one odorant from another. At page 3 of the specification, it is stated that "the present inventors have uncovered polymorphic OR genes which exhibit loss or reduced function in receptor capacity." However, the specification does not teach a particular biological activity associated with the OR11H7p pseudogene or any of the additional genes and allelic variants thereof set forth in the present specification. For example, the specification does not disclose a particular ligand/odorant that binds to the ORs or a particular odor detected by individuals having the OR11H7p pseudogene or any of the additional OR genes recited in the specification. Thereby, the specification has not taught one of skill in the art how to use a OR gene having a loss or reduced function, and particularly the OR gene of OR11H7p, for a specific and substantial purpose because the specification does not disclose a specific activity that is lost or reduced in the OR11H7p gene or the other genes of Table 5.

The specification (page 3) further states that "(t)the present inventors have also demonstrated that the occurrence of these allelic variations differ in individuals from different ethnic backgrounds thereby suggesting that polymorphism in OR genes contributes to differences in smell perception of individuals." However, the specification does not teach a clear nexus between any particular OR polymorphisms and the phenotype of smell perception. Further, a specific type of "smell perception" is not disclosed in the specification. The general concept of a loss of OR function and smell perception constitutes a nonspecific activity that could potentially be associated with any OR protein. To establish a specific and substantial activity for the OR allelic variants would require a showing that the presence of the OR allelic variant is associated with a particular type of smell perception.

While the specification teaches that the OR allelic variants can be used for typing individuals, the specification does not clearly teach how one can use the information obtained from typing. The use of the OR allelic variants to determine their functional activity is not considered to be a substantial utility because this utility essentially involves performing research in order to find a utility for the polymorphisms, i.e., in order to establish that the polymorphisms are associated with a phenotype. As stated in Brenner v. Manson, 383 U.S. 519 535-536, 148 USPQ 689, 696 (1966) " a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion". Support for an asserted utility that is specific and substantial would require, for example, a showing of a particular function for the OR allelic variants, or a showing of a clear correlation between the disclosed OR allelic variants and the occurrence of a particular condition. Identifying and studying the properties of the allelic variant and its frequency in different ethnic populations. polymorphisms or performing assays to determine a correlation between the polymorphisms and disease does not constitute a "real world" context of use.

Note, because the claimed invention is not supported by a specific and substantial asserted utility for the reasons set forth above, credibility has not been assessed. Neither the specification as filed nor any art of record discloses or suggests any property or activity for the OR allelic variants such that another non-asserted utility would be well established for the compounds.

Accordingly, the claimed invention is not supported by either a specific or substantial asserted utility or a well-established utility. Applicant is directed to the Utility Examination Guidelines, Federal Register, Vol. 66, No. 4, pages 1092-1099, Friday January 5, 2001.

Response to Remarks:

In the response, Applicants traverse this rejection by stating that a declaration by the inventor "accompanied by new experimental data (Appendix A) which was obtained following filing of the instant application" has been filed. It is asserted that the declaration establishes the utility and enablement of the claimed invention. Applicants assert that the specification states that the disclosed genotype is associated with the phenotype of olfactory perception. It is further asserted that the declaration establishes that isovaleric acid is the odorant of the OR11H7p olfactory receptor and that the C to T point mutation at position 679 of the coding sequence of the receptor (position 691 of SEQ ID NO: 81) can be used to predict olfactory sensitivity to this odorant. Applicants conclude that the declaration merely confirms what was stated in the originally filed specification that there is a correlation between the genotype and phenotype of olfactory perception.

The Declaration of Dr. Doron Lancet states that the C to T mutation at position "379 of OR11H7P (SEQ ID NO: 81) is linked to hypersomia to isovaleric acid. The declaration further sates that supplementary Figure 2 "suggests that sensitivity to isovaleric acid is generally indicative of olfactory sensitivity."

These arguments and the declaration of Dr. Doron have been fully considered but are not persuasive to overcome the present grounds of rejection.

It is first noted that the declaration refers to position "379 of OR11H7P (SEQ ID NO: 81)", whereas Appendix A refers to position 679 of OR11H7P (position 691 of SEQ ID NO: 81). Thereby, the statements set forth in the declaration do not pertain to the same mutation presently claimed and for which data is presented at page 10 of Appendix A.

Secondly, Applicants assertion that the C to T mutation at position 691 of SEQ ID NO: 81 is correlated with sensitivity to the odorant isovaleric acid is not supported by the

specification as originally filed. The U.S. Court of Appeals for the Federal Circuit recently addressed the utility requirement as it applies to nucleic acids. See In re Fisher 421 F.3d 1356, 76 USPQ2d1225 (Fed. Cir. 2005). The Court held that 35 USC 101 requires a showing that a nucleic acid is both substantial and specific. The court emphasized that disclosing a substantial utility means "show[ing] that an invention is useful to the public as disclosed in its current form, not that it may be useful at some further date after further research. Simply put, to satisfy the 'substantial' utility requirement, an asserted use must show that claimed invention has a significant and presently available benefit to the public." Id. 76 USPQ2d at 1230. In the present situation, the originally filed specification does not disclose an association between the C691T mutation in SEQ ID NO: 1 and hypersomia to the specific odorant isovaleric acid. Rather, the specification stated only that there was a general association between this mutation and "olfactory perception." Further, the data set forth in the declaration indicates that only individuals homozygous for the 691T allele are associated with hypersomia to isovaleric acid. However, the specification as originally filed did not disclose this specific association and thereby does not provide support for this specific utility.

The response and declaration further assert that the data in Supplementary Figure 2 "suggests that sensitivity to isovaleric acid is generally indicative of olfactory sensitivity." However, the data presented in the declaration do not support the broadly asserted utility that the C691T mutation in SEQ ID NO: 81 is associated with any type of olfactory perception. Rather, the data presented in the declaration in fact establish that

the mutation is not correlated with response to the odorants isoamyl acetate, carvone and cineole. While Supplementary Figure 2 demonstrates an inter-oderant threshold for the 4 tested odorant pairs, it has not been established that this showing is sufficient to indicate that the C691T mutation is associated with response to the vast number of possible odorants and thereby can be considered to be an indicator of all olfactory perception.

The declaration states that the typing of a subject with respect to olfactory perception has many uses, including screening for employment positions. However, the rejection is not based on a general lack of use for a method for determining a subject's response to an odorant. Rather, the rejection is based on the finding that the specification as originally filed did not disclose an association between the C691T mutation and response to a particular odorant. The post-filing date data obtained by Applicants establishing that individuals homozygous for the 691T allele are sensitive to the odorant isovaleric acid is not sufficient to establish the specific utility of the claimed invention at the time the invention was made because this association was not set forth in the specification as originally filed.

The following grounds of rejection was originally set forth in the Office action of March 27, 2007 and has been modified to accommodate the amendments to the claims:

Claim Rejections - 35 USC § 112 - Enablement

6. Claims 23, 24, 28 and 34 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and

substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention.

Additionally, the specification has not enabled one of skill in the art to practice the claimed methods for the reasons that follow. The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

Claims 23, 24 and 28 are drawn broadly to encompass methods for typing a subject according to the presence or absence of an allelic variant of an olfactory receptor (OR) gene "as set forth in SEQ ID NO: 81" using a probe "as set forth in SEQ ID NO: 29." The specification does not define the phrase "as set forth" in SEQ ID NO: 81 or 29. Accordingly, this phrase has been given its broadest reasonable interpretation as including OR genes and probes which include portions of SEQ ID NO: 81 and 29, respectively, flanked by nucleotides of any identity and length. The claims do not set forth any particular allelic variant of SEQ ID NO: 81 that is to be detected by the recited method. Further, the claims do not define the overall structure of the OR gene since the claims encompass OR genes which include only a portion of SEQ ID NO: 81. Thereby, the claims encompass detecting a significantly large genus of allelic variants of the OR gene of SEQ ID NO: 81 and other OR genes containing portions of SEQ ID NO: 81.

Further, claim 34 does not define the particular methodology which is used to type the subject. Thereby, the claims encompass any means for detecting the allelic variant, including methods which indirectly detect the allelic variant by performing an activity assay or by detecting a polymorphism that is in linkage disequilibrium with the allelic variant.

Nature of the Invention

The claims are drawn to methods for typing a subject based on the presence or absence of an allelic variant in an olfactory receptor gene. The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Teachings in the Specification and State of the Art:

The specification (Tables 5 and 6) discloses the OR genes of SEQ ID NO: 79-104, teaches a single nucleotide polymorphism present in each of these genes and teaches allele specific probes that hybridize to the stated polymorphisms. With respect to the elected invention, the specification teaches the allelic variant of a C to a T at nucleotide position 691 of OR11H7p gene of SEQ ID NO: 81 (Table 5 and 6). The specification also teaches the allele specific oligonucleotide probe of SEQ ID NO: 29 which detects the T variant allele and the allele specific oligonucleotide probe of SEQ ID NO: 3 which detects the C variant allele. Table 5 indicates that the presence of a T at nucleotide position 691 introduces a premature stop codon into the OR11h7p gene. In provisional application 60/374,508, the OR11h7p nucleic acid is characterized as a

segregating pseudogene (see Table I, page 62 therein). The specification further teaches the frequency of the intact and disrupted allele in Table 5 in African American subjects and in non-African American subjects. In Table 5, the specification also sets forth a number of additional olfactory receptor genes, an allelic variant form of said genes and the frequency of intact and disrupted alleles in African American subjects and in non-African American subjects.

The specification (page 1) teaches that there are about 400 functional olfactory receptor (OR) genes in humans and that the diversified OR repertoire is needed to allow individuals to detect and discriminate between thousands of different odorant molecules. The specification (page 2) also teaches that ORs interact with a diverse array of volatile molecules and that this binding pattern generates a unique combinatorial code for each odorant that enables an organism to distinguish one odorant from another. At page 3 of the specification, it is stated that "the present inventors have uncovered polymorphic OR genes which exhibit loss or reduced function in receptor capacity." However, the specification does not teach a particular biological activity associated with the OR11H7p pseudogene or any of the additional genes and allelic variants thereof set forth in the present specification. For example, the specification does not disclose a particular ligand/odorant that binds to the ORs or a particular odor detected by individuals having the OR11H7p pseudogene or any of the additional OR genes recited in the specification.

Since the specification has not disclosed a particular biological activity or physiological effect of the C to T allelic variant of OR11H7p, the specification has not taught one of skill in the art how to use the claimed method of typing a subject for the C to T polymorphism for a practical purpose.

Further, the specification has not taught one of skill in the art how to practice the claimed methods by detecting any allelic variant in SEQ ID NO: 81 using a probe that comprises any portion of SEQ ID NO: 29 under any set of hybridization conditions. The specification has also not taught one of skill in the art how to predictably detect allelic variants of homologues of SEQ ID NO: 81 in non-human subjects using a probe comprising any portion of SEQ ID NO: 29.

The Predictability or Unpredictability of the Art :

The art of determining an association between a polymorphism and a phenotype is highly unpredictable.

The teachings of Lucentini (The Scientist. December 2004, page 20) highlights the unpredictability in the art of establishing an association between a polymorphism and the occurrence of a disease or condition. As discussed by Lucentini, reproducible association studies are "few and far between." The reference reports that "when a finding is first published linking a given gene with a complex disease, there is only roughly a one third chance that studies will reliably confirm the finding. When they do, they usually find the link is weaker than initially estimated. The first finding is usually 'spurious, or it is true, but it happens to be really exaggerated, ' ...there may be no way to predict which new gene-association studies will be verified with multiple replication."

Moreover, the claims encompass detecting an OR allelic variant in any subject. However, the specification does teach the occurrence of any OR allelic variants in non-human subjects. In particular, the specification does not teach a gene homologous to the OR11H7p gene in a representative number of non-human subjects and the

occurrence of allelic variants in this gene in a representative number of non-human subjects. No information is provided regarding the biological effects of the C to T polymorphism on the functional activity of an OR protein or on the occurrence of any specific phenotype. Without extensive information regarding the structure-function relationship between this polymorphism and a specific phenotype, it is highly unpredictable as to whether the OR11H7p gene and the C to T polymorphism therein will occur in non-human subjects and will be associated with a particular phenotype.

Amount of Direction or Guidance Provided by the Specification and Degree of Experimentation:

The specification does not provide sufficient guidance as to how to detect additional allelic variants of OR genes and establish an association between the occurrence of the allelic variants and particular phenotypes or biological activities. Extensive experimentation would be required to identify additional polymorphisms in SEQ ID NO: 81 and determine their biological effect. For example, such experimentation may involve sequencing the OR11H7P gene in subjects having particular olfactory phenotypes, such as subjects with specific anosmias which lack the ability to perceive particular odorants, sequencing the same gene in a control group of subjects which are able to perceive particular odorants, comparing the nucleotide sequence of the test group with that of the control group, and performing a statistical analysis to determine whether there is a statistically significant increase or decrease in the occurrence of a particular polymorphism in the test group versus the control group and vice versa. The experimentation may also include performing the above method by

analyzing any of the wide multitude of other phenotypes that may be associated with an olfactory receptor gene. Additionally, the experimentation may include performing methods to try to identify a ligand that binds to the allelic variant or the wildtype OR gene in order to try to develop a biological activity assay that could be used to indirectly detect the allelic variant. Further experimentation may also include performing linkage analysis to try to identify a polymorphism that is in full linkage disequilibrium with an allelic variant and which could thereby be used to infer the presence of the allelic variant. The outcome of such experimentation cannot be predicted and is thus considered to be undue.

While methods for sequencing nucleic acids are known in the art, such methods provide only the general guidelines that allow researchers to randomly search for polymorphisms that may linked to a particular phenotype. The results of performing such methodology are highly unpredictable. The specification has provided only an invitation to experiment. The specification does not provide a predictable means for identifying additional polymorphisms associated with particular phenotypes in a representative number of human or non-human subjects.

Working Examples:

The specification provides a working example in which human subjects having a T at nucleotide position 691 of SEQ ID NO: 81 are detected.

No working examples are provided wherein the presence of a T at nucleotide position 691 of SEQ ID NO :81 is detected as indicative of a particular phenotype, biological activity or other type of physiological effect.

No working examples are provided wherein other allelic variants of SEQ ID NO: 81 are detected as indicative of olfactory perception.

No working examples are provided wherein non-human subject's are analyzed for the presence of an allelic variant in an OR gene comprising a portion of SEQ ID NO: 81.

No working examples are provided wherein the T at nucleotide position 691 of SEQ ID NO: 81 is indirectly detected by performing, for example, an activity assay or by assaying for the presence of a polymorphism in linkage disequilibrium with the T691 allelic variant.

Conclusions:

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, the specification has not taught one of skill in the art how to use the claimed invention without undue experimentation because the specification does not disclose any particular biological activities or physiological effects or any conditions associated with the occurrence of the C691T OR11H7p polymorphism or any of the other disclosed polymorphisms. Further, the claims do not bear a reasonable correlation to the scope of enablement because the specification does not teach a representative number of OR genes and OR allelic variants in humans and in a representative number of non-human subjects in order to enable the broadly claimed methods of typing any human or non-human subject for the presence of any allelic variant in any OR gene. Also, the specification does not teach each of the novel aspects of the claimed invention because the novelty of the claimed invention lies in the identity of the particular OR genes and the particular allelic variants therein. The novel aspects of the invention are not general methods of sequencing OR genes since such methods were conventional in the art at the time the invention was made. Accordingly, although the level of skill in the art of molecular biology is high, given the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the invention as broadly claimed.

Response to Remarks:

In the response, Applicants traverse this rejection for the same reasons stated in paragraph 5 above. Accordingly, the response to those arguments apply equally to the present grounds of rejection. Further, the rejection is maintained because claims 23, 24 and 28 as broadly written include detecting any allelic variant in SEQ ID NO: 81. The claims do not specifically require detecting a T at position 691 in the OR11H7P gene of SEQ ID NO: 81. Rather, the claims recite detecting an allelic variant of an OR gene "as

set forth in SEQ ID NO: 81" using a probe "as set forth in SEQ ID NO: 29." The specification does not define the phrase "as set forth" and therefore this phrase has been broadly interpreted as including nucleic acids which consist of or comprise SEQ ID NO: 29 or 81 and nucleic acids which comprise any fragment of SEQ ID NO: 29 or 81, flanked by any number of nucleotides of any identity. Thereby, the claims still encompass methods which detect any allelic variant of an OR gene, wherein the OR gene is not specifically defined and the allelic variant is also not specifically defined in terms of its particular nucleotide sequence. Further, claim 34 does not define the particular methodology which is used to type the subject. Thereby, the claims encompass any means for detecting the allelic variant, including methods which indirectly detect the allelic variant by performing an activity assay or by detecting a polymorphism that is in linkage disequilibrium with the allelic variant.

The following grounds of rejection was originally set forth in the Office action of March 27, 2007 and has been modified to accommodate the amendments to the claims:

Claim Rejections - 35 USC § 112- Written Description

7. Claims 23, 24 and 28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

Claims 23, 24 and 28 are drawn broadly to encompass methods for typing a subject according to the presence or absence of an allelic variant of an olfactory receptor (OR) gene "as set forth in SEQ ID NO: 81" using a probe "as set forth in SEQ ID NO: 29." The specification does not define the phrase "as set forth" in SEQ ID NO:

81 or 29. Accordingly, this phrase has been given its broadest reasonable interpretation as including OR genes and probes which include portions of SEQ ID NO: 81 and 29, respectively, flanked by nucleotides of any identity and length. The claims do not set forth any particular allelic variant of SEQ ID NO: 81 that is to be detected by the recited method. Further, the claims do not define the overall structure of the OR gene since the claims encompass OR genes which include only a portion of SEQ ID NO: 81. The claims do not set forth the conditions for hybridization and thus the claims encompass methods which detect any allelic variant in any nucleic acid that hybridizes to some degree to SEQ ID NO: 29, or portions thereof, under low stringency hybridization conditions. Thereby, the claims encompass detecting allelic variants in any functional OR gene and pseudogene comprising a portion of SEQ ID NO: 81, in any human or non-human subject (e.g., rat, dog, monkey, elephant etc). As set forth on page 1 of the specification there are at least about 400 functional ORs in humans. The number of ORs in other mammals is considered to be even higher, given the enhanced olfactory facilities of some species. The claims do not define the allelic variant in terms of any particular function or structure – i.e., gene in which it is present, nucleotide position, or nucleotide identity. Thereby, the claims encompass detecting a significantly large genus of allelic variants of OR genes, wherein the allelic variants are not defined in terms of a particular structure or function.

The specification (Tables 5 and 6) discloses the OR genes of SEQ ID NO: 79-104, teaches a single nucleotide polymorphism present in each of these genes and teaches allele specific probes that hybridize to the stated polymorphisms. With respect

to the elected invention, the specification teaches the allelic variant of a C to a T at nucleotide position 691 of OR11H7p gene of SEQ ID NO: 81 (Table 5 and 6). The specification also teaches the allele specific oligonucleotide probe of SEQ ID NO: 29 which detects the T variant allele and the allele specific oligonucleotide probe of SEQ ID NO: 3 which detects the C variant allele.

Thereby, while the allelic variant of a T at nucleotide position 691 of SEQ ID NO: 81 meets the written description requirements of 35 U.S.C. 112, first paragraph, the specification does not disclose and fully characterize the broadly claimed genus of any allelic variant of any OR gene or any allelic variant of an OR gene of SEQ ID NO: 79-104.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that 'applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the

court states that 'An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the specification teaches 26 specific allelic variants present in the OR genes of SEQ ID NO: 79-104. However, this disclosure is not considered to be representative of the broadly claimed genus of any allelic variant present in the OR gene of any organism. The claimed genus is considered to be potentially extremely large since it may comprise an allelic variant at any nucleotide position within any of the potential 400 or more genes present in any organism. Further, the specification discloses allelic variants only in human OR genes. No allelic variants in a representative number of non-human OR genes have been described. Additionally, each of the allelic variants described in the specification consists of a single nucleotide or dinucleotide polymorphisms. No allelic variants have been described which include larger deletions, substitutions or deletions in OR gene sequences. Thereby, the disclosure of 26 specific polymorphisms in 26 specific human OR genes is not considered to be representative of the broadly claimed genus of any allelic variation in any human or non-human OR gene. It is then determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g. restriction map, biological activity of an encoded protein

product, etc.). In the instant case, no such identifying characteristics have been provided for the allelic variants.

However, as discussed above, the claims as written are inclusive of a potentially large genus of allelic variants. While one could contemplate possible polymorphisms or other nucleotide additions, deletions or substitutions at each and every position in the human OR genes of SEQ ID NO: 79-104 and in any and all other OR genes of human and non-human organisms, such nucleotide variations are not considered to be equivalent to specific nucleotide variations associated with a particular phenotype or effect. Rather, polymorphisms in OR genes represent a distinct group of nucleotide variations that are expected to occur at only specific locations within OR genes and consist of specific nucleotide alterations. Accordingly, knowledge of the sequence of wild-type OR genes does not allow the skilled artisan to envision all of the contemplated allelic variations encompassed by the claimed genus.

Given the limited amount of structural information regarding allelic variants of OR genes, one of skill in the art cannot envision the detailed chemical structure of the nucleic acids encompassed by the claimed methods, regardless of the complexity or simplicity of the method of identification. Adequate written description requires more than a mere statement that analysis of such nucleic acids are part of the invention and reference to a potential method for identification. The particular nucleic acids themselves are required.

For these reasons, Applicants have not provided sufficient evidence that they were in possession, at the time of filing, of the invention as it is broadly claimed and

thus the written description requirement has not been satisfied for the claims as they are broadly written. Applicants attention is drawn to the Guidelines for the Examination of Patent Applications under 35 U.S.C. 112, ¶ 1 'Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Response to Remarks:

In the response, Applicants traverse this rejection by stating that the claims are directed to a method for determining whether there is a C or a T at a specific position in an OR sequence and particularly are limited to detected a specific mutation in SEQ ID NO: 81 at position 679.

This argument has been fully considered but is not persuasive. The claims are not in fact limited to the detection of a C or a T at position 679 of SEQ ID NO: 81. Claims 23, 24 and 28 do not define the location of the allelic variant and do not identify the allelic variant as being a C or a T. Further, the claims recite the broad claim language of detecting the allelic variant in a OR gene "as set forth in SEQ ID NO: 81" using a probe "as set forth in SEQ ID NO: 29." Because the phrase "as set forth" has not been clearly defined in the specification, this phrase has been given its broadest reasonable interpretation as including OR genes and probes that comprise any portion of any length of SEQ ID NO: 81 or 29, flanked by nucleotides of any length and identity. Thereby, Applicants are arguing limitations not recited in the claims because the claims are not limited to methods for detecting the presence of a C or T at position 691 of a nucleic acid consisting of SEQ ID NO: 81 using a probe consisting of SEQ ID NO: 29.

The following grounds of rejection was originally set forth in the Office action of March

27, 2007 and has been modified to accommodate the amendments to the claims:

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 23, 24, 28 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bellenson in view of NCBI SNP Database (rs1953558, January 3, 2001).

Bellenson teaches a method of sequencing an OR nucleic acid comprising a sequence that is identical to present SEQ ID NO: 81 (referred to therein as SEQ ID NO: 555) wherein said nucleic acid is obtained from a biological sample of a subject (see, e.g., pages 17-18 and 43-46). The nucleic acid of Bellenson contains a T at nucleotide

position 691 (see page 226). Accordingly, the method of Bellenson is considered to be one that detects the presence of an allelic variant of an OR gene in a biological sample of a subject, wherein detection of the presence of an allelic variant thereby types the subject. Bellenson teaches an OR gene (SEQ ID NO: 555 therein) that is identical to present SEQ ID NO: 81 and which contains a T at nucleotide position 691 of SEQ ID NO: 81. Bellenson (e.g., claim 33) further teaches methods for detecting polymorphisms in said OR gene. The reference also teaches polynucleotide probes which hybridize to and detect OR gene sequences (see page 12). Bellenson does not specifically teach methods for detecting a polymorphism in the OR gene of SEQ ID NO: 81 (SEQ ID NO: 555 therein) wherein said polymorphism is detected using a probe comprising present SEQ ID NO: 29.

However, the NCBI SNP database teaches that nucleotide position 691 of present SEQ ID NO: 81 contains a C to T polymorphism:

CATTCTGTGA GCTCTCTTTT CATCAACCTC ACCATGGTGT ACATCCTTGG GTCCTATACC
TTGGTGCTCA GAACTGTGCT T
Y
AGGTTCCTTC TTCAGCTGGA TGGCAAAAGG CCATCTCTAC CTGTGGGTCA CACTTGGTTG
TTGTGTCTCT GTTCTATGGA GCCATAATGC TGATGTATGT GAGTCCCACA CCTGGCAACT

In view of the teachings of the NCBI SNP database of the occurrence of a C to T polymorphism at position 691 and the teachings of Bellenson of methods for detecting polymorphisms in the stated OR gene and of the use of probes for detecting such polymorphisms, it would have been obvious to one of ordinary skill in the art at the time

the invention was made to have modified the method of Bellenson so as to have used a probe comprising the sequence of present SEQ ID NO: 29 to detect the presence of the allelic variant of a T at nucleotide position 691 of SEQ ID NO: 81 (SEQ ID NO: 555 therein) in order to have provided an effective means for detecting this polymorphism and for typing individuals. While Bellenson does not teach a probe that specifically consists of SEQ ID NO: 29, Bellenson does teach generating probes to detect a target nucleic acid sequence and teaches the nucleotide sequences flanking the C to T polymorphism disclosed by the NCBI SNP database. Further, the parameters and objectives involved in the selection of allele specific probes were well known in the art at the time the invention was made. Moreover, software programs were readily available which aid in the identification of conserved and variable sequences and in the selection of optimum probes. The prior art is replete with guidance and information necessary to permit the ordinary artisan to design probes for detecting the C to T polymorphism, including the probe of present SEQ ID NO: 29. Accordingly, use of the probe of SEQ ID NO: 29 in the method of Bellenson for detecting a polymorphism would have been obvious to one of ordinary skill in the art at the time the invention was made. Additionally, regarding claim 34, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Bellenson so as to have detected the presence of a C to T variation at position 691 of SEQ ID NO: 81 since NCBI SNP database discloses the occurrence of this mutation and such a modification would have allowed one of ordinary skill in the art to detect the occurrence

of the polymorphism to further determine its frequency and would have allowed for the typing of individuals with respect to the presence of this polymorphism.

Regarding claim 24, in the method of Bellenson, the OR genes are detected in a biological sample of the subject by amplifying RNA of the subjects and analyzing the amplification products by sequencing. (see pages 43-46).

Regarding claim 28, in the method of Bellenson, the presence of the allelic variant is determined by analyzing mRNA (see page 43).

Response to Remarks:

In the response, Applicants traverse this rejection by stating that Bellenson does not teach typing a subject according to olfactory perception. However, modification of the method of Bellenson as set forth above results in a method which includes the same method step recited in the present claims – i.e., a method which detects an allelic variant in a OR gene using a probe of SEQ ID NO: 29 (claims 23, 24, and 28) and a method which detects a C to T variation at position 691 of SEQ ID NO: 81. The claims recite that the single step of detecting this variation results in the typing of a subject regarding its olfactory perception. Since the method steps are the same, the method of Bellenson must also necessarily result in the typing of a subject with respect to their olfactory perception. The present claims do not recite any particular step which distinguishes the claimed method over that of Bellenson – e.g., a step in which the detection of a T at position 691 of SEQ ID NO: 81 is indicative of increased sensitivity to a particular odorant. The claims merely state a characterization or conclusion of the results of the step of detecting. Thus, the recitation of "thereby typing the subject with

regard to the subject's olfactory perception" does not distinguish the claimed method over that suggested by Bellenson in view of the NCBI SNP database. See Texas Instruments, Inc. v. International Trade Comm., 988 F.2d 1165, 1171, 26 USPQ2d 1018, 1023 (Fed Cir. 1993) ("A 'whereby' clause that merely states the result of the limitations in the claim adds nothing to the patentability or substance of the claim."). See also Minton v. National Assoc. of Securities Dealers, Inc., 336 F.3d 1373, 1381, 67 USPQ2d 1614, 1620 (Fed. Cir. 2003) ("A whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited.").

New grounds of rejection necessitated by applicant's amendments to the claims:

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 23, 24, 28 and 34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 23, 24 and 28 are indefinite over the recitation of "the allelic variant" because this phrase lacks proper antecedent basis.

Claims 23, 24, 28 and 34 are indefinite over the recitation of "thereby typing the subject with regard to the subject's olfactory perception." The claims recite a single step of detecting an allelic variant or a C to T variation and conclude that this single step results in the typing of a subject with respect to their olfactory perception. However, it is unclear as to how the detection of an allelic variant by itself results in the typing of a

subject with respect to their olfactory perception. Thereby, it is unclear as to what is intended to be encompassed by "typing a subject with respect to olfactory perception." For example, it is unclear as to whether such typing merely refers to the detection of a T or C at position 691or whether such typing refers to determining a particular response of a subject to any or all odorants. In the later case, the claims appear to omit essential elements and steps required to practice the claimed method because the claims do not set forth how the detection of an allelic variant or a T or C at position 691 results in the determination of a particular response to any or to all odorants.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is 571-272-0747. The examiner can normally be reached on Monday-Thursday (6:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Carla Myers/

Primary Examiner, Art Unit 1634